REMARKS/ARGUMENTS

Claims 39-44, 46-51, 60 and 66 are pending in this application. Re-examination and reconsideration of the pending claims are respectfully requested.

Amount of Drug (Gregory US 5,283,257)

Applicants maintain that the amount of drug disclosed by Gregory is 10,000 fold the applicant's amount. Examiner has stated that "...the milligrams disclosed, is per kilogram of implant carrier, therefore, the actual drug amount present would be less than a millimeter [sic], since a stent weighs no where near a kilogram." Applicants would like to point out that the doses that Gregory is referring to is mg per kilogram *weight* of the subject, whether it is a rat or a human. E.g., Gregory notes that the MPA dosage would be about 500 to 4,000mg/day—clearly many orders of magnitude more than what is contemplated by the applicants—5 to 200μg/day. Examiner notes that the amounts disclosed by Gregory are for MPA and that Mizorbine is used in combination with MPA. Gregory provides no indication about the amounts of Mizorbine to be used, but one skilled in the art would reasonably infer that if MPA is delivered in the 100s of mg quantity, an accompanying drug would also be delivered in a similar amount and not 4 orders of magnitude less—100s of mg vs. μg—as contemplated by applicants. i.e., the amount of Mizorbine described in Gregory will also be in the mg quantities and not microgram quantities.

Rejections under 35 USC § 112

Claim 50 has been amended and new claim 66 has been added to overcome the rejections under 35 USC § 112.

Rejections under 35 USC § 103

Claims 39-44, 48-49 and 60 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gregory et al., U.S. Patent No. 5,283,257 (hereinafter referred to as Gregory). This rejection is respectfully traversed for the following reasons.

As the Examiner knows and appreciates, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references, alone or in combination, must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. M.P.E.P. § 2142; *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants respectfully maintain that a *prima facie* case of obviousness has not been established.

Gregory fails to teach or suggest all of the claim limitations. Independent claim 60 recites, in part, that "...mizoribine from the prosthesis into the blood vessel at a rate between 5 μg/day to 200 μg/day so as to inhibit smooth muscle cell proliferation, wherein substantial release of mizoribine is delayed for at least one hour following implantation of the prosthesis. The μg/day quantities is not disclosed in Gregory. The Examiner appears to agree. Furthermore, the delayed release is not disclosed in Gregory. In fact, Gregory does not disclose in detail a stent based pharmaceutical preparation. The pharmaceutical preparations disclosed by Gregory are powders, tablets (col. 7, line 64), liquid carriers (col. 8, lines 4-22), suppository (col. 8, ll. 47-48), and transdermal patches (col. 8, line 50). As the Examiner notes, Gregory describes testing different amount to arrive at the optimal dose. However, the *precise dosages are determined by the administering physician based on experience with the individual subject treated* (col. 9, lines 12-14). In Claim 60, the release rate is dictated by the prosthesis, not by the physician.

Claims 39-44, 48-49 and 60 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Brown et al. US 6,071,305 (hereinafter referred to as Brown) in view of Gregory. Claims 39-44, 48-49 and 60 have also been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ragheb et al. US 6,774,278 (hereinafter referred to as Ragheb) in view of Gregory.

Brown describes a *directional drug delivery stent with a fluid opening* (col. 6, lines 6-7). Brown uses the size and the shape of the cavity to control the amount of the active agent and the rate of delivery (col. 8, lines 26-28). Applicant's claimed invention does not rely on the presence of a fluid opening, does not directionally deliver the drugs and the delivery rate is not controlled by the size and shape of the cavity.

The Examiner asserts that "...the drug will be delayed to get to the surface or exit the stent, because it takes time to travel through the diffusion barrier or for the degradable matrix to degrade or dissolve and inherently there will be a delay of release from the stent." There has been no support provided by the Examiner for this statement. This is true only if the coating or release means is devoid of any drug. If there is a diffusion barrier that is devoid of the drug, there will likely be a delay (the drug will have to traverse this diffusion barrier and that will lead to a delay in the drug exiting the stent). However, Applicants are unable to identify which diffusion barrier the Examiner is referring to. Even if it were assumed that there is a rate controlling membrane or barrier present, Brown does not indicate whether there is any drug present in the matrix. If the drug is in equilibrium in the different layers of the release means, including the surface, it is likely that the drug will exit immediately following the implantation. If the diffusion barrier is the arterial wall, the Examiner is correct that it will take time for the drug to diffuse through this diffusional barrier. However, in Brown, there is no description of an intentional delay in substantial release of the drug, as described in Claim 60. As the Examiner has acknowledged, neither Brown nor Gregory disclose the release rates of Claim 60 and more particularly neither describe the intentional delayed release. The Examiner attempts to cure these deficiencies by arguing that these features are inherent in Brown. But as the Examiner is certainly aware, inherences requires that the failure or result must necessarily be present, not just could be present. No such showing has been made.

Ragheb describes a method for preventing the degradation of a drug by coating a protective layer on a device, which could be a stent. The coating could be porous and be a polymer to provide controlled release of the drug. Ragheb does not disclose the release of mizorbine at the desired 5 µg/day to 200 µg/day as described in claim 60 and certainly not the intentional delay in release of mizorbine following the implantation of the prosthesis..

As the Examiner has acknowledged, neither Ragheb nor Gregory disclose the release rates of Claim 60 and more particularly neither describe the intentional delayed release. However, the Examiner has combined these two references to reject claim 60 and 39-44, and 46-51 that depend on claim 60.

There is no suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings so as to produce the claimed invention.

As *Prima facie* obviousness has not been established for the several reasons set forth above, Applicants respectfully request that the rejection of independent claim 60 be withdrawn and the claim (including all claims dependent thereon) be allowed.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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